Chapter 11

The Emerging Neurobiology of Dissociation: Implications for Treatment of Posttraumatic Stress Disorder

John H. Krystal, M.D., J. Douglas Bremner, M.D.,
Steven M. Southwick, M.D., and Dennis S. Charney, M.D.

Despite progress in identifying, characterizing, and quantitatively assessing dissociative states, there has been surprisingly little study of their neurobiology. Associated with the failure to elucidate a unique neurobiology for dissociative states, there have been few placebo-controlled pharmacotherapy trials for dissociative disorders and no specific antidissociative drugs developed. The absence of antidissociative pharmacotherapies contrasts with the development of anxiolytics, antiobsessionals, antipsychotics, mood-stabilizing agents, and antidepressants. In light of the paucity of research in this area, the commonly held view that core features of dissociative disorders are unresponsive to pharmacotherapy is not surprising (Kluft 1987).

In this chapter, we review recent progress made in studying the neurobiology of dissociative states in posttraumatic stress disorder (PTSD) patients. It is possible, given the elevated prevalence of early traumatic experiences in other dissociative disorders, that

This work was supported by funds from the Department of Veterans Affairs to the National Center for Posttraumatic Stress Disorder, the Veterans Administration-Yale Alcoholism Research Center, and the Merit Review Grant Program (JHK).

studies of dissociation in PTSD patients will have broader implications for patients with other dissociative disorders (see Chapter 12 in this volume). In this chapter, we focus on studies that have produced dissociative states in healthy individuals and patients with PTSD or other neurological disorders. In doing so, we attempt to highlight bridges between the neurobiology and treatment of PTSD.

Guided Recollection: Narcosynthesis and the Amytal Interview

The medical facilitation of traumatic memory recall and flashbacks in traumatized individuals began in World War II as part of a therapeutic approach called narcosynthesis or, more recently, the "Amytal interview." This approach combined barbiturates and guided recollection of traumatic memories (Bartemeier et al. 1946; Grinker and Spiegel 1945; Sargent and Slater 1940). The use of barbiturates to facilitate traumatic memory recall was illustrated by a case reported by Grinker (1944):

> That afternoon I gave him 0.25 Gm. of pentothal sodium intravenously. He was then told that he was up in the air on a strafing mission and that the man on his wing was aflame. . . . Immediately he [shouted] to his friend . . . "pull up and bail out. Why doesn't he pull up and bail out?" . . . he went over and over the traumatic situation, crying and sobbing. As this reaction subsided he was allowed to close his eyes and sleep . . . [upon awakening] He stated "I must have been asleep. I had a dream about [my friend]". . . . (pp. 142-143)

Facilitating traumatic memory recall by barbiturates and benzodiazepines is paradoxical; drugs with prominent amnestic effects improve aspects of memory function. These drugs impair attention and memory in humans (Kirk et al. 1990; Krystal et al. 1995). However, their amnestic effects arise primarily through interfering with memory encoding rather than memory storage or retrieval (Ghoneim and Mewaldt 1990). Mechanisms through which

barbiturates and benzodiazepines facilitate the recollection of traumatic memories and flashbacks are poorly understood. They enhance the actions of gamma-aminobutyric acid (GABA) at the $GABA_A$ receptor (Olsen 1981), and barbiturates additionally block the actions of glutamate at non-*N*-methyl-D-aspartate (non-NMDA) receptors (Collins and Anson 1987; Morgan et al. 1991). However, barbiturates are not specific in their capacity to facilitate recollection of traumatic memories in that ether, ethanol, nitrous oxide, and scopolamine-morphine combinations also appear to facilitate the recall of inaccessible memories (Erickson 1945; Rosen and Meyers 1947).

The prodissociative effects of these drugs are indirect. Benzodiazepines, for example, do not increase scores on scales measuring dissociation in healthy individuals (J. H. Krystal, L. P. Karper, D. C. D'Souza, et al: "Interactive Effects of Subanesthetic Ketamine and Lorazepam in Humans: Psychotomimetic, Dissociative, Cognitive, and Neuroendocrine Responses," unpublished manuscript, 1997). Clinical observations suggest that the sedating and anxiolytic medications employed in narcosynthesis reduce anxiety and thus may lessen the resistance to recalling anxiety-associated memories (Grinker and Spiegel 1945). This view is consistent with a patient who experienced flashbacks during relaxation training (Fitzgerald and Gonzalez 1994). Alternatively, these medications, viewed as "truth serums" by the popular press, may suppress involuntary mechanisms responsible for reducing voluntary access to traumatic memories (Kardiner and Spiegel 1947). Related to this hypothesis, recent physiological research has provided additional evidence of a neural basis for directed forgetting and other processes associated with reduced voluntary access to established memories (Geiselman et al. 1983; Paller 1990). A recent case study evaluating the neuropsychological consequences of psychogenic amnesia supported the view that guided recollection under the influence of Amytal reduced the capacity of active processes outside of voluntary control to reduce the level of awareness of learned information or memory of events (Kopelman et al. 1994).

Pharmacological Challenge Studies in Patients With Posttraumatic Stress Disorder

Flashbacks have been precipitated in Vietnam veterans with chronic PTSD following the intravenous administration of sodium lactate (Rainey et al. 1987), yohimbine (Southwick et al. 1993), and metachlorophenylpiperazine (m-CPP; Southwick et al. 1991). Administration of each of these substances produces panic attacks in a significant proportion of patients with either panic disorder (Charney et al. 1984, 1987; Pitts and McClure 1967) or PTSD (Rainey et al. 1987; Southwick et al. 1991, 1993) but not other patient groups. However, PTSD patients are the first group studied to experience flashbacks following administration of these substances.

Rainey et al. (1987) compared the response to intravenous sodium lactate, isoproterenol, and a dextrose placebo in seven Vietnam combat veterans, six of whom also met criteria for panic disorder. All seven patients experienced flashbacks following lactate, two patients also experienced flashbacks after isoproterenol infusion, and one patient experienced a flashback during placebo infusion. The authors described these flashbacks as similar to those occurring naturally as part of PTSD. Six of the seven lactate-induced flashbacks, both isoproterenol flashbacks, and the dextrose flashback were followed by paniclike states. However, the absence of reported anxiety ratings makes it impossible to determine whether subpanic increases in anxiety preceded the flashbacks. The overlap of panic disorder and PTSD in patients in this study was another limitation because it raised concerns that lactate-induced flashbacks were a property of panic disorder and not independently associated with PTSD. Little is known about the mechanisms through which lactate produces panic attacks and flashbacks in PTSD patients.

The precipitation of flashbacks and panic attacks in PTSD patients by yohimbine linked noradrenergic systems, implicated in fear and arousal regulation, to the symptoms of PTSD (Southwick et al. 1993). Yohimbine activates central noradrenergic neurons through blockade of α_2 receptors located on noradrenergic neurons. These α_2 receptors mediate, in part, feedback inhibition of

noradrenergic neurons (Starke et al. 1975). Following yohimbine, 40% (8 of 20 patients) experienced flashbacks and 70% (14 of 20 patients) experienced panic attacks. No panic attacks and only one flashback emerged following placebo administration. Although 45% of the patients in this study also met DSM-III-R (American Psychiatric Association 1987) criteria for panic disorder, 43% of the yohimbine-induced panic attacks occurred in individuals without panic disorder. The risk of a yohimbine-induced panic attack was increased in patients with panic disorder relative to those without comorbid panic disorder (89% versus 43%). However, history of panic disorder did not appear to influence the likelihood of experiencing a yohimbine-induced flashback.

The following vignette illustrates features of a yohimbine-induced flashback:

> 10:00 A.M.: [Initiation of yohimbine infusion]
>
> 10:05 A.M.: Subject reports hot and cold flashes, goose bumps, palpitations
>
> 10:10 A.M.: Subject reports clammy hands, he asked the nurse to move away from him . . . in case he felt like running. "I feel like I'm picking up dead bodies . . . the centrifuge sounds like a helicopter . . . A chopper is shooting at us, we're trying to shoot back at it! One of the guys' head is shot off! Brains are coming at me! I smell burnt flesh . . . I feel scared, I can't hear what's going on . . . ."

The operational definition for flashback employed in Southwick et al. (1993) led to the exclusion of many dissociative states produced by yohimbine in the PTSD patients. The following criteria were employed to define a drug-induced flashback: 1) the reexperiencing of a past traumatic event during drug infusion, 2) the reexperiencing must involve one or more sensory modalities, and 3) for patients with a history of flashbacks, the drug-induced state must be similar to naturally occurring flashbacks. Despite the expedient characterization of flashbacks as being present or absent, yohimbine actually produced a continuum of dissociative phenomena. Patients experienced varying degrees of derealization

and depersonalization that were often accompanied by other dissociative symptoms. Yohimbine also elicited a range of altered perceptual experiences, some of which were fragmentary or vague. For example, one patient perceived the shadow produced by a sink in the testing facility to be the shadow made by a tank turret. In addition to stimulating flashbacks, yohimbine significantly increased the recall of traumatic memories. Although yohimbine produced symptoms of autonomic arousal in many patients, these symptoms were not the sole predictor of flashbacks within a session. Yohimbine also significantly increased the recall of traumatic memories. In some cases, symptoms of autonomic arousal followed or were coincident with the reported retrieval of traumatic memories (S. M. Southwick, personal communication, May 1994). Thus, it appeared that noradrenergic systems might be involved in the elicitation of dissociative symptoms as a direct consequence of the central pharmacological actions of yohimbine on neural circuitry contributing to dissociation and memory retrieval. These data contrasted with models in which noradrenergic contributions to PTSD symptoms were entirely mediated by peripheral autonomic systems.

The yohimbine study suggested that activation of noradrenergic systems by yohimbine produced panic attacks and flashbacks in a subset of PTSD patients. One question raised by this study was whether the elicitation of flashbacks by yohimbine reflected a specific response to α_2 receptor blockade or whether all anxiogenic drugs produce flashbacks in PTSD patients. To investigate this question, yohimbine and m-CPP effects were compared in this population (Southwick et al. 1991). This study found that both m-CPP and yohimbine produced flashbacks and other dissociative states in veterans with combat-related PTSD. Preliminary analyses indicated that patients tended to experience panic attacks following yohimbine or m-CPP, but not both medications. As with the initial study, drug-induced traumatic memories, autonomic activation, and anxiety states could be associated with the induction of flashbacks, although no single response preceded flashbacks in all cases. These observations raised the possibility that yohimbine and m-CPP caused flashbacks by modulating a final common

pathway that has yet to be identified or that multiple mechanisms might lead to the induction of flashbacks.

To continue the search for key neurotransmitter systems involved in dissociation in PTSD patients, we studied the effects of the benzodiazepine antagonist flumazenil in PTSD patients. This drug failed to precipitate flashbacks or panic attacks in PTSD patients (Randall et al. 1995). As with lactate, yohimbine, and m-CPP, flumazenil has been reported to produce panic attacks in patients with panic disorder (Woods et al. 1991). The absence of flumazenil-induced panic attacks and flashbacks in PTSD suggests that flumazenil is not associated with the overproduction of an endogenous benzodiazepine-inverse agonist, such as a diazepam-binding inhibitor, which might contribute to anxiety symptoms in other disorders (Costa and Guidotti 1987). Future studies will be needed to determine whether benzodiazepine-inverse agonists, such as FG 7142 or iomazenil, which precipitate anxiety in healthy subjects (Dorow et al. 1983; Randall et al. 1995) will produce flashbacks in PTSD patients.

Case reports suggest that alcohol and opiate withdrawal may increase PTSD symptoms, including flashbacks (Kosten and Krystal 1988; Salloway et al. 1990; J. P. Seibyl, personal communication, May 1994). Central noradrenergic systems are activated during alcohol and opiate withdrawal, suggesting a possible parallel between yohimbine- and withdrawal-induced flashbacks (Kosten and Krystal 1988).

Induction of Dissociative States in Healthy Individuals

Pathophysiological models that hypothesize a "final common pathway" for the neurobiology of dissociation presuppose that modulation of the activity of this pathway might produce dissociative states in healthy individuals. To date, three classes of drugs commonly produce dissociative-like states in healthy subjects: 1) antagonists of the NMDA subtype of glutamate receptor, 2) cannabinoids, and 3) serotonergic hallucinogens.

The non-competitive NMDA receptor antagonist anesthetics, phencyclidine and ketamine, produce a derealized and depersonalized state characterized by marked perceptual alterations and psychosis at subanesthetic doses (Domino et al. 1965; Javitt and Zukin 1991; Luby et al. 1959; Yamakura et al. 1993). The capacity of ketamine to produce dissociative-like states in healthy subjects has been rigorously evaluated in a series of studies (Krystal et al. 1994a, 1994b). In these studies, dissociative symptoms were rated using the Clinician-Administered Dissociative States Scale (CADSS; Bremner et al., in press). At low blood levels, ketamine produced a light-headed feeling. With higher blood levels of ketamine, subjects reported the slowing of time and alterations in the vividness, form, and context of sensory experiences. For example, subjects noted that objects appeared brighter or duller than expected, larger or smaller than usual, and distorted in shape or with altered proximity. Also, some subjects had difficulty hearing someone speaking close to them, although they reported that a radio playing quietly in the next room sounded unusually loud. Altered proprioceptive experiences were reported by subjects who felt that their limbs changed form or were floating in air.

Cognitive effects of ketamine also were prominent. Subjects reported constriction of their field of attention, resulting in the sensation of tunnel vision or the feeling that they were surrounded by fog. For example, subjects attending to a computer keyboard frequently lost track of events happening on the computer monitor. Ketamine also produced learning and memory impairments. Its effects increased proportionately to the dose administered and the duration of delay between stimulus presentation and testing. In addition, ketamine interfered with executive functions such as abstraction, assessed by proverb interpretation, and problem solving, evaluated by the Wisconsin Card Sorting Test (Heaton 1985). Although subjects felt that they had lost control of their thought processes, with effort they could focus on tasks.

Ketamine also produced emotional responses. At low doses, it had mild anxiolytic properties, whereas larger doses generally produced euphoria and anxiety. Anxiety stimulated by ketamine tended to follow perceptual alterations and thought disorganiza-

tion and tended to be related to the subjects' degree of comfort with the drug-induced disturbances in thought and perception. Some subjects found the perceptual alterations produced by ketamine quite pleasurable, analogous to a ride in an amusement park, whereas others found the effects of ketamine frightening.

Ketamine-induced insight impairments and identity-related responses may have contributed to the elicitation of anxiety. Following drug infusion, some subjects lost the perspective that their mental status change was produced by ketamine, and they became concerned that they had contracted a mental illness. Transient identity alterations also were observed with ketamine. For example, a subject who received ketamine (0.26 mg/kg intravenous bolus followed by 0.65 mg/kg/hr) stated, "At first it seemed that I didn't exist, I couldn't process information; after a while, I was convinced that I was an organism, then I realized I was a human being, then after a longer while I remembered that I was a medical student." Ketamine did not lead to the emergence of multiple personalities, flashbacks, or vivid intrusive memories in research subjects. However, symptoms associated with psychosis, including delusions and thought disorder, were observed during ketamine infusion.

Two ongoing studies have attempted to pharmacologically alter ketamine-induced dissociative states by pretreating healthy subjects with lorazepam or haloperidol (Krystal et al. 1994a; (J. H. Krystal, L. P. Karper, D. C. D'Souza, et al., "Interactive effects of subanesthetic ketamine and lorazepam in humans," unpublished manuscript, 1997). Preliminary data from these studies suggested that lorazepam 2 mg administered orally 2 hours before ketamine administration tended to reduce altered environmental perceptions but had no effects on other dissociative symptoms or psychotic states produced by ketamine. Haloperidol failed to reduce dissociative symptoms, vigilance impairments, or amnestic effects produced by ketamine but reduced ketamine-induced distractibility, abstraction impairments, and bizarreness of thought processes. These data suggested that at the doses tested neither agent is a true ketamine antidote. They are also consistent with the literature suggesting that neuroleptics have

limited efficacy in treating dissociative symptoms (Kluft 1987).

To date, there have not been formal evaluations of the effects of ketamine in PTSD patients or patients with other dissociative disorders. However, anecdotal data from Russian studies suggest that ketamine induces dissociative states and may promote guided recollection of traumatic material in Russian Afghanistan war veterans with PTSD (Krupitsky 1972, personal communication, January 1994).

Dissociative states also have been produced by psychoactive cannabinoids, such as tetrahydrocannabinol, the principal psychoactive component of marijuana and hashish. Cannabinoids bind to a specific G-protein-coupled receptor (Herkenham et al. 1990) through which they alter cellular functions, including blockade of N-type calcium channels, inhibition of cyclic adenosine monophosphate (cAMP) accumulation, and stimulation of arachidonic acid and intracellular calcium release (Felder et al. 1993). Some cannabinoid effects may be mediated by stimulation of glucocorticoid receptors (Eldridge and Landfield 1990) and blockade of NMDA receptors (Feigenbaum et al. 1989). At high doses, cannabinoid intoxication produces depersonalization, derealization, temporal disorientation, perceptual alterations, and insight impairments (Bromberg 1939; Dittrich et al. 1973; Melges et al. 1970). Depersonalization and temporal disorientation produced by marijuana smoking were associated with increased cortical regional cerebral blood flow assessed with the ^{133}xenon inhalation technique (Mathew et al. 1993). Cannabis has been reported to produce flashbacks that resemble cannabis intoxication in drug-free subjects (Hollister 1986). In one study (Stanton et al. 1976), 3% (1 of 31) of habitual marijuana users and 1% (3 of 348) of nonhabitual users reported flashbacks when drug-free, suggesting that flashbacks were not a frequent consequence of cannabis use. However, this study suggested that marijuana use also enhanced the likelihood of experiencing flashbacks following ingestion of the serotonergic hallucinogens.

Serotonergic hallucinogens, such as lysergic acid diethylamide (LSD), mescaline, and dimethyltryptamine (DMT), also produce dissociative symptoms. These agents stimulate serotonin-2 (5-HT_2) receptors (Rasmussen et al. 1986; Titeler et al. 1988). Serotonergic

hallucinogens produce pronounced visual hallucinations, illusions, synesthesia, and expansive or portentous emotional responses (Freedman 1968; Strassman et al. 1994). Following ingestion of psychedelics, subjects report prominent feelings of derealization or depersonalization. Environmental stimuli may be experienced in a fragmented manner, body image distortion is common, and feelings of emotional detachment may arise (Freedman 1968; Klee 1963; Liebert et al. 1958; Rodin and Luby 1966; Savage 1955). Some clinicians also have reported that LSD may facilitate the recall of repressed memories (Freedman 1968), although this capacity has never been rigorously evaluated. Relative to the phencyclidine or ketamine experience, psychedelic hallucinogens tend to produce perceptual effects that predominate over dissociative effects and impairments in higher cognitive functions.

Flashbacks have been reported in healthy individuals following serotonergic hallucinogen use. Freedman (1968) and Horowitz (1969) suggested that LSD intoxication was traumatic for some users because it diminished control over awareness, resulting in intense emotional states experienced as beyond their control. In such cases, LSD flashbacks might have a traumatic etiology. However, some LSD-like experiences, such as synesthesia, may be reexperienced long after drug ingestion by individuals who find such experiences pleasant. These effects do not easily fit a trauma model, suggesting that sensitization, conditioning, or state-dependent learning also might apply (Freedman 1968, 1984; Horowitz 1969; McGee 1984). Subject expectancy also may play a role in druglike flashbacks. One study found that flashbacks may be produced in healthy subjects following placebo administration if subjects are coached to anticipate that a placebo will produce flashbacks (Heaton 1975). Heaton suggested that the expectancy of flashbacks led subjects to mislabel and selectively attend to aspects of normal experience that are consistent with a flashbacklike experience.

Lessons From Brain Stimulation Studies

Flashbacks are common to PTSD and conditions associated with local activation of cortical and limbic structures. Hughlings Jackson

first described the complex polysensory reexperiencing of events that occurred in association with temporal lobe epilepsy as memory flashbacks (Taylor 1931). Patients with clinical and encephalographic evidence of temporal lobe epilepsy exhibited a range of dissociative symptoms, including depersonalization, derealization, auditory and visual hallucinations, and multiple personalities (Mesulam 1981b). Sacks (1985) also described a patient with seizure foci in her medial temporal structures that produced repetitive reexperiencing of Irish folk melodies. Anticonvulsant treatment eliminated the intrusive musical reexperiencing but also eliminated her ability to recall the melodies.

Penfield and Perot (1963) elicited dreamlike states, memories, and complex experiential phenomena through direct electrical stimulation of structures in the temporal lobe, temporoparietal association areas, hippocampus, and amygdala. Temporal lobe stimulation resulted in some individuals reexperiencing frightening events in a polysensory fashion, such as a possible thwarted kidnapping (see case 15 in Penfield and Perot 1963). However, neutral or pleasant experiences also were produced, such as hearing a choir sing "White Christmas" (see case 4 in Penfield and Perot 1963). The amygdala and hippocampus appear to be implicated in the experiential phenomena associated with temporal lobe activation. Gloor et al. (1982) found that experiential phenomena were associated with direct stimulation of the amygdala and the hippocampus. Moreover, memories, dreamlike states, or other complex experiential phenomena were produced only when temporal cortical stimulation was followed by afterdischarges in the amygdala or hippocampus. Results of this study were consistent with an earlier one that produced complex experiential phenomena through electrical stimulation of the hippocampus and amygdala (Halgren et al. 1978).

The brain stimulation studies suggest that the hippocampus and amygdala control the retrieval of memory in a highly specific manner, much as a program might control access to information stored on a computer. However, this interpretation appears overly simple. Complex experiential phenomena are usually associated with high-intensity stimuli or afterdischarges, suggesting that

fairly large cortical areas must be activated (Halgren et al. 1978). Also, stimulation of the same location over several trials does not reliably reproduce experiential phenomena, whereas stimulation of disparate cortical regions may produce identical experiences (Halgren et al. 1978; Horowitz et al. 1968). In addition, surgical excision of an area that produces a memory when directly stimulated does not eliminate the memory (Baldwin 1960). A more circumspect interpretation of these data is that memory is stored within distributed networks and that the amygdala and hippocampus stimulations bias the retrieval of memories in a more general fashion, such as facilitating access to an associative network.

One of the striking similarities of flashback associated with PTSD and the brain stimulation studies are the inflexible nature of memory retrieval under these conditions. Dreams and memories often replay traumatic scenes in their entirety rather than being retrieved with the cognitive flexibility characteristic of declarative memory. The neurobiology underlying the loss of retrieval flexibility and efficiency associated with traumatic memory retrieval, limbic stimulation studies, and the developmental disorders is currently unclear. However, reduced mnemonic flexibility has been reported to characterize memory retrieval under conditions where the hippocampus is activated independently of the frontal cortex (Moscovitch 1992). Memory encoding by the hippocampus is modular, and organizing links between memories arise largely through cue association, as occurs during conditioning (Moscovitch 1992). Retrieval strategies involving the hippocampus are cue dependent and not strategic. In other words, the hippocampus cannot efficiently scan stored memories to retrieve a particular memory, even though it is involved in memory encoding. The organizing and strategizing component of memory retrieval appears to depend on the frontal cortex (Moscovitch 1989, 1992). Thus, flashbacks may share the qualities of memory retrieval exhibited by individuals during hippocampal stimulation because these conditions involve retrieval strategies that bypass the frontal component of memory retrieval despite relative preservation of the hippocampal component of memory retrieval.

Recollective processes that bypass frontal executive mecha-

nisms controlling the strategic recollection of information also may share the quality of being reexperienced rather than recalled. Flashbacks produced by electrical stimulation in seizure patients (Penfield and Perot 1963) and those occurring in PTSD (Bremner et al. 1992; Southwick et al. 1991) were both described in this manner. Frontal cortical networks have been implicated in executive functions related to the control of memory retrieval (Baddeley 1986). Frontal lobe lesions, unlike hippocampal lesions, impair retrieval of autobiographical information (Baddeley and Wilson 1988). The frontal cortex also has been implicated in prioritizing responses, generating mental representations within working memory, self-monitoring, and editing of thought (Baddeley 1986; Goldman-Rakic 1987; Stuss 1992). The frontal cortex is nested within networks involving the amygdala, mediodorsal thalamic nucleus, hippocampus, and other regions that provide access to input regarding the nature and meaning of memories that are formed (Goldman-Rakic 1987). Sedative-hypnotic agents produce impairments on tests sensitive to frontal cortical impairment, as does ketamine (Krystal et al. 1994a; J. H. Krystal, L. P. Karper, D. C. D'Souza, et al., "Interactive Effects of Subanesthetic Ketamine and Lorazepam in Humans," unpublished manuscript, 1997).

Thalamic Networks and Dissociative States

Dissociative states occur normally in individuals without dissociative disorders when they are exposed to conditions of extremely low or high levels of sensory stimulation. Reductions in the intensity or variability of sensory stimulation, associated with hypnosis, sleep deprivation, and sensory deprivation, may produce altered states of consciousness with dissociative features (Bexton et al. 1954; Cappon and Banks 1960; Freud and Breuer 1892/1953; Lilly 1956; Krystal 1988). As an extreme illustration of this point, sensory polyneuropathies may cause marked depersonalization and derealization associated with feelings of being disembodied (Sacks 1985). Heightened sensory stimulation or arousal also may produce altered sensory processing. Significant levels of arousal and anxiety heighten the salience and vividness of environmental stimuli.

When individuals are under stress, attention is narrowed to the most salient aspects of the environment, consistent with the need to focus on the danger at hand. Thus, individuals fixate faster and longer on unusual or highly informative objects, such as weapons (Christianson 1992; Christianson and Loftus 1991), whereas less critical but important information about the context of the trauma may not receive much attention (Kramer et al. 1990). At extremely high levels of arousal, coherent integration of sensory information breaks down and dissociative symptoms emerge, even in individuals without dissociative disorders (Cappon and Banks 1961; Ludwig 1972; Krystal et al. 1988, 1991).

The thalamus plays a critical role in modulating responsivity to environmental stimuli associated with sleep and dreaming and may play a similar role in the genesis of dissociative states. As illustrated in Figure 11-1, the thalamus serves as a sensory gate or filter that directly and indirectly modulates the access of sensory information to the cortex, amygdala, and hippocampus (Amaral and Cowan 1980; McCormick 1992; Steriade and Llinás 1988; Turner and Herkenham 1991). During slow-wave sleep, for example, thalamic nuclei exhibit slow spindle oscillations that disrupt the transmission of sensory information to cortical and limbic structures (Steriade and Deschenes 1984). During wakefulness, thalamic neurons fire in a relay mode that facilitates transmission of sensory information to cortical regions. Rapid eye movement (REM) sleep, associated with dreaming, is characterized by phasic enhancement of the activity of glutamatergic thalamocortical cells (Steriade and McCarley 1990; Steriade et al. 1990). In this model, dreams and other sleep-related internally generated experiences may arise as thalamocortical or other direct cortical projections from the amygdala and hippocampus bypass the oscillatory thalamic processes that disrupt the flow of sensory information to the cortex (Llinás and Paré 1991; Swanson 1981). Thus, like dissociative states, sleep states may neurobiologically preserve associative and mnemonic functions while interrupting sensory processing. Sensory processing alterations associated with dissociative states could indicate the intrusion of sleep-related disturbances in sensory processing into the waking state. If so, then alterations in tha-

lamic activity might link a spectrum of altered states of consciousness such as hypnosis, dreaming, and other conditions in which there is a combination of the features of sleep and waking states (Llinás and Paré 1991; Mahowald and Schenck 1991). Dissociative states also might be related to night terrors in which features of waking behavior intrude on sleep (Fisher et al. 1973; Kales et al. 1980; Oswald and Evans 1985). Evidence for a thalamic role in maintaining the boundary of sleeplike behavior and wakefulness is provided by patients with paramedian thalamic infarctions. These patients exhibit a profound sense of detachment, reduced responsivity to sensory stimuli, and sleeplike posturing throughout the circadian cycle without the electrophysiological correlates of non-REM sleep (Guilleminault et al. 1993). The hypothesis that the thalamus contributes to dissociation-like alterations in consciousness is further supported by thalamic activation during absence seizures (Prevett et al. 1995).

A role of the thalamus in dissociation also is suggested by its distinctive function in modulating the onset of night terrors. Posttraumatic nightmares occur within REM sleep and are not generally associated with motor behaviors, although they may repetitively review aspects of the trauma (Fisher et al. 1970, 1973; Greenberg et al. 1972). In contrast, posttraumatic night terrors bear a closer resemblance to flashbacks occurring in the waking state. Night terrors are associated with confusion upon awakening, reduced responsivity to environmental stimuli, displays of intense emotion, significant autonomic activation, increased sleep motility, complex motor activity, and somnambulism (Fisher et al. 1970, 1973; Hafez et al. 1987; Lavie and Hertz 1979; van der Kolk et al. 1984). Despite behavioral evidence that traumatic incidents are being reexperienced during night terrors, such as calls for help and appearing to act out physical struggles, individuals are generally amnestic for the content of their experiences. As with flashbacks and nightmares, night terrors may be precipitated in PTSD patients by reminders of the trauma or environmental stress (Fisher et al. 1970; Krystal 1968). Unlike nightmares, night terrors occur during deep sleep, particularly stage 4, and generally within the

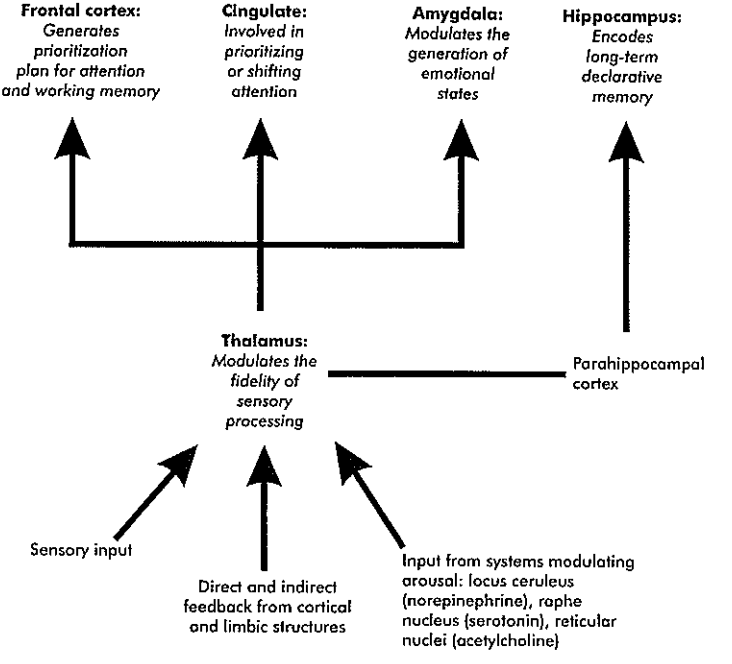

Figure 11–1. Position of the thalamus within networks that may be involved in the generation of dissociative states. Sensory information reaches the thalamus and is transmitted to limbic and cortical regions responsible for modulating thought, attention, learning and memory, and emotion. The thalamus receives input from limbic regions, such as the amygdala, and brain stem regions involved in stress-related arousal. It also receives direct and indirect feedback from cortical regions involved in prioritizing attention. When functioning in relay mode, the thalamus facilitates the accurate transmittal of sensory information. However, when slow oscillatory firing patterns predominate, the thalamus impedes the flow of sensory information to cortical and limbic regions associated with the predominate focus on internally generated thought processes and sensory experiences associated with dreaming, night terrors, and perhaps dissociation.

Krystal JH, Bennett A, Bremner JD, et al: "Toward a Cognitive Neuroscience of Dissociation and Altered Memory Functions in Post-Traumatic Stress Disorder," in *Neurobiological Consequences of Stress From Adaptation to Post-Traumatic Stress Disorder.* Edited by Friedman M, Charney DS, Deutch AY. New York, Raven, 1995. Reprinted with permission.

first hour after falling asleep (Fisher et al. 1973; Kales et al. 1980). Nightmares and night terrors may be further distinguished by the effects of paramedian thalamic lesions. These lesions eliminate the stages of sleep that contain night terrors but do not alter REM sleep and dreaming (Guilleminault et al. 1993).

Sensory distortions associated with stress may develop, in part, as a consequence of the thalamic role in modulating sensory processing. Thalamic nuclei appear to work both in series and in parallel with brain regions involved in traumatic stress response. One region that may be critical for fear learning and traumatic stress response is the central nucleus of the amygdala (Charney et al. 1993; M. Davis 1992; LeDoux 1987). Once activated by uncontrollable stressors, the central nucleus of the amygdala facilitates the thalamic relay of sensory information to cortical and limbic structures (Clugnet and LeDoux 1990; Steriade et al. 1990).

Central noradrenergic systems also are activated by significant uncontrollable stressors and have been linked to traumatic stress response (Krystal et al. 1989; Bremner et al. 1996a, 1996b). Stress-induced noradrenergic activation would be expected to facilitate thalamic transduction of sensory information by stimulating thalamic α_1-adrenergic receptors that increase thalamic activity associated with wakefulness and to inhibit slow thalamic oscillations (Buzsáki et al. 1990; McCormick and Wang 1991). Postsynaptic α_2 receptors promote thalamic slow oscillations. Thus yohimbine, an α_2 antagonist, could increase thalamic bursting by increasing norepinephrine release and blocking the stimulation slow oscillations produced by postsynaptic α_2 receptors (Buzsáki et al. 1990).

Serotonergic systems, linked to PTSD symptoms by the m-CPP study described previously (Southwick et al. 1993), also heighten sensory processing via the 5-HT_2 receptor (McCormick and Wang 1991). Both m-CPP and the serotonergic hallucinogens stimulate subtypes of this receptor (Sheldon and Aghajanian 1991). Perceptual alterations associated with extreme or uncontrollable stress suggest that massive activation of monoamine systems under these conditions may modulate thalamic function, resulting in interference rather than enhancement of the fidelity of sensory transmission.

Alterations in thalamic glutamatergic function also could contribute to sensory gating disturbances. Glutamate is the primary excitatory neurotransmitter within the thalamus (McCormick 1992) and the neurotransmitter involved with thalamic afferents from the amygdala, cerebral cortex, and hippocampus (Aggleton and Mishkin 1984; Aggleton et al. 1986; Giguere and Goldman-Rakic 1988; LeDoux and Farb 1991; McCormick 1992). Indirect cortical thalamic modulation also occurs via a circuit involving the striatum, globus pallidus, subthalamic nucleus, and thalamus (Carlsson and Carlsson 1990). Both NMDA and non-NMDA glutamate receptors are localized to the thalamus, where they have complementary functions (McCormick 1992). Previous reviews have suggested that alterations of the sensory filter function of the thalamus via blockade of NMDA receptors could contribute to the psychotomimetic effects of the NMDA antagonists (Carlsson and Carlsson 1990). These hypotheses may be consistent with electrophysiological evidence indicating that the thalamus may be particularly sensitive to the proconvulsant effects of subanesthetic doses of NMDA antagonists (Ferrer-Allado et al. 1973).

Given the prominent role of non-NMDA glutamate receptors in corticostriatothalamic circuitry, subanesthetic doses of selective NMDA antagonists might be predicted to produce distortions rather than complete blockade of thalamic sensory gating functions. This prediction is consistent with clinical observations suggesting that ketamine produces a state of detachment or withdrawal rather than sleep. Also, ketamine produces sensory distortions and illusions rather than blockade of sensory perceptions or pure hallucinatory experiences (Krystal et al. 1994b). The capacity of sensory deprivation to reduce rather than augment the behavioral effects of phencyclidine further suggests that NMDA antagonists alter rather than block sensory processing (B. D. Cohen et al. 1960). Future research is needed to clarify the extent of thalamic contributions to dissociative states.

The thalamus is a heterogeneous structure, and component thalamic nuclei have distinctive cortical afferents and efferents and different patterns of synaptic organization (M. L. Schwartz et al. 1991). For example, the reticular nuclei of the thalamus

function in some ways as an extension of brain stem and midbrain reticular activating systems (Steriade and Llinás 1988). However, other thalamic nuclei, such as the anteroventral and mediodorsal nuclei, appear to be involved in associative processes, such as learning (Gabriel et al. 1987, 1991; Orona and Gabriel 1983).

Sensory processing alterations and changes in attention may be linked in dissociative states. Clinically, the bridge between sensory gating and attention modulation is evident in the reduced responsivity to environmental stimuli exhibited by dissociated individuals and their reported focus on peripheral sensory stimuli or internal mental processes (Carlson and Putnam 1989). This connection also is suggested by the convergence of corticolimbic networks on the anterior cingulate gyrus, a brain region implicated in the capacity to shift and focus attention (Bench et al. 1993; Pardo et al. 1990). Anterior cingulate lesions may produce symptoms reminiscent of thalamic, limbic, and cortical lesions, including confusion, vivid daydreaming, apathy, impairments in sustained attention, and learning impairments (Laplane et al. 1981; Whitty and Lewin 1957). Direct projections to the anterior cingulate gyrus from midline and intralaminar thalamic nuclei suggest that the cingulate gyrus is responsive to shifts in thalamic sensory processing functions (Vogt et al. 1979). As suggested by the clinical case reports of patients with cingulate lesions, the cingulate gyrus also may be involved in the attribution of salience and the acquisition and retrieval of learned information (Gabriel et al. 1991; Gaffan et al. 1993). The contributions of the cingulate gyrus to sensory processing, emotional regulation, and learning are facilitated by its connectivity to other brain regions. For example, hippocampal and anteroventral thalamic inputs converge upon the anterior cingulate gyrus via the posterior cingulate gyrus (Gabriel and Sparenborg 1987; Gabriel et al. 1987). Similarly, the anterior cingulate gyrus is an important point of convergence for a network involving the amygdala, prefrontal cortex, and mediodorsal thalamic nucleus (Aggleton and Mishkin 1984; Gaffan and Murray 1990; Gaffan et al. 1993; Goldman-Rakic and Porrino 1985; Orona and Gabriel 1983).

Cortical Dysconnectivity and Dissociation

Geschwind (1980) wrote, "there is no evidence for the existence of any all-purpose computer in the brain." Consistent with this view, cortical functions are highly distributed across several cortical regions that require integration to generate coherent conscious experience. For example, frontoparietal interactions help to locate memories or mental representations in space, frontohippocampal interactions appear to contribute contextual information regarding these memories, and frontotemporal interactions contribute to working memory for shapes and features (A. Belger, G. McCarthy, J. Gore, "FMRI Studies of Working Memory Networks: Parietal and Temporal Lobe Studies," unpublished manuscript, 1996; Goldman-Rakic 1987). Also, the frontal cortex itself contains many functionally heterogeneous regions. Distinct frontal cortex loci mediate the generation of iconic or working memories for the location and features of environmental stimuli. Brain lesions of one region of the frontal cortex result in memory gaps for spatial features, whereas lesions of the other region produce an inability to recall faces (Goldman-Rakic 1987; Wilson et al. 1993). If corticocortical interactions were disturbed or disrupted, experiences and cognitive functions that depend on integrated cortical activity might be distorted. For example, if frontal cortical regions processing features of objects and their spatial attributes were interacting dysfunctionally, one might generate mental representations for stimuli in which features were not correctly matched to their spatial locations (i.e., objects could be experienced out of context or in bizarre or incoherent ways). Disturbances in function arising from abnormal integration of cortical function may be similar, by analogy, to conduction aphasias. In conduction aphasias, both comprehension and fluency are preserved, but speech is paraphasic because information cannot be effectively transmitted from association to motor cortices (Geschwind 1970).

Drugs that produce dissociative states disturb cortical integration at several levels. The key output neurons of the cortex are pyramidal neurons that use glutamate as their primary neurotransmitter. These neurons are regulated locally by modulatory

GABAergic neurons. Pyramidal neurons also receive distant input from subcortical monoaminergic, glutamatergic, and peptidergic systems and glutamatergic input from pyramidal neurons in other cortical areas (Goldman-Rakic 1987; Lewis et al. 1992). In the piriform cortex, serotonergic hallucinogens inhibit pyramidal neuronal activity by stimulating GABAergic interneurons via the 5-$HT_{2A/2B}$ receptors. However, these drugs also activate pyramidal neurons through stimulating 5-HT_{2C} receptors (Sheldon and Aghajanian 1991).

Subanesthetic doses of ketamine distort the functional connectivity within the cortex by blocking the NMDA receptor-mediated component of glutamatergic corticocortical connectivity. One study, for example, suggested that blockade of NMDA receptors allowed sensory information to reach the cortex but interfered with the coherent transmission of this information from receptive areas to association cortices (Corssen and Domino 1966). Ketamine may produce these disturbances by altering the balance of glutamate receptor stimulation, decreasing the stimulation of NMDA receptors, and increasing non-NMDA glutamate receptor stimulation. Subanesthetic doses of ketamine preferentially reduce the activity of inhibitory cortical interneurons, disinhibiting cortical pyramidal neurons and increasing glutamate release (Dingledine et al. 1986; Moghaddam and Bolinao 1994). Enhancing GABA function reduces the dissociative effects of ketamine, consistent with the hypothesis that facilitating GABA function might reduce the consequences of decreased interneuronal activation. Blockade of non-NMDA glutamate receptors also might be predicted to reduce ketamine effects because glutamate released as a result of ketamine administration will bind to those glutamate receptor subclasses not blocked by ketamine (i.e., non-NMDA receptors). Barbiturates weakly but significantly block two non-NMDA glutamate-receptor subclasses, the amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate receptors (Collins and Anson 1987; Morgan et al. 1991), and might be evaluated for their capacity to reduce ketamine effects.

Recent data also may implicate shifts in interhemispheric processing in hypnotic and dissociative experiences. In particular, re-

cent studies report that hypnosis is associated with performance reductions on tests sensitive to impairments of the left frontal cortex (Gruzelier and Warren 1993). Hypnosis also may be associated with lateralized shifts in electroencephalogram frequency and evoked potential amplitudes (Spiegel 1991). The hypothesis that interhemispheric processing alterations contribute to dissociative states also is supported by a recent report of two cases in which alternate personalities were differentially elicited in patients with multiple personality disorder with temporal lobe epilepsy through administration of intracarotid amobarbital selectively to the two cortical hemispheres (Ahern et al. 1993).

Alteration in Glutamatergic Function: A Final Common Pathway for Dissociation?

Clinical studies related to the neurobiology of dissociative states are summarized in Table 11-1. Yohimbine and m-CPP produce dissociative states only in PTSD patients, who are prone to have these experiences. These drugs primarily produce dissociative states while stimulating anxiety or traumatic recollections. Thus, yohimbine and m-CPP may not directly induce dissociation but rather contribute to the modulation of networks, resulting in a dissociative state in vulnerable individuals. In the amygdala, hippocampus, thalamus, and cortex, noradrenergic and serotonergic systems serve to modulate the activity of glutamatergic neurons (Goldman-Rakic 1987; Lewis et al. 1992). Given the central role of glutamate in corticocortical, thalamocortical, amygdalocortical, and hippocampocortical connectivity, glutamatergic systems in the brain may be considered the framework on which higher cognitive functions rest. Thus, it may not be surprising that a drug, such as ketamine, that alters glutamatergic neurotransmission produces dissociative states in healthy individuals. The possibility that glutamate systems might be fundamentally involved in generating dissociative states is consistent with the observation that dissociative states produced by ketamine in healthy people arise as a direct consequence of drug administration and are not dependent on gener-

Table 11–1. Summary of pharmacologically facilitated dissociative states

Substance	Healthy subjects	PTSD patients
Yohimbine	–	+
m-CPP	–	+
Lactate	–	+
Sedative-hypnotics	–	+[a]
Benzodiazepine antagonists	–	–
NMDA antagonists	+	+[b]
Cannabinoids	+	?
Serotonergic hallucinogens	+	?

Note. PTSD = posttraumatic stress disorder; m-CPP = metachlorophenylpiperazine; NMDA = *N*-methyl-D-aspartate; – = not associated with dissociative state; + = associated with dissociative state; ? = unclear association with dissociative state.

[a]Facilitation of dissociation during guided recollection.

[b]Not formally evaluated in patients with PTSD.

ating intense emotional responses or memories. The direct evocation of dissociative states by an NMDA antagonist raises the possibility that reductions in NMDA receptor function contribute to dissociative states in humans. If so, then pharmacological agents that enhance NMDA receptor function might have antidissociative properties (Jones et al. 1991; Nicholls 1993; Saletu et al. 1986; B. L. Schwartz et al. 1991).

Implications for the Treatment of Posttraumatic Stress Disorder

Dissociative phenomena, traumatic memories, and affective regulation are highly interrelated in PTSD patients Bremner et al. 1993). Traumatic memories and intense emotions may trigger dissociative phenomena in PTSD patients. Similarly, traumatic memories become more accessible when emotional or dissociative states resembling those at the time of traumatization are produced. Completing the triangle, traumatic memories and dissociative phenomena may precipitate strong emotional responses. Thus, reducing the inci-

dence of flashbacks and the intrusiveness and distress related to traumatic memories must be understood in the context of treating each of the three interactive processes.

The first step in treating dissociative states in traumatized individuals is to alleviate the marked depersonalization, derealization, and extreme emotional arousal. Barbiturates and benzodiazepines may be useful for this purpose (Kluft 1987). The long-term benefits of acute anxiolysis are currently unclear. However, Kardiner (1941) emphasized the importance of the peritraumatic period in creating a long-lasting appraisal of traumatic events. Acute anxiolysis may be helpful in reducing negatively valenced cognitive distortions. Thus, in the context of supportive therapy, benzodiazepine treatment may facilitate the development of a more adaptive appraisal of the traumatic stress, perhaps by altering pairing of emotions and memories. Benzodiazepines also may prevent other stress-related alterations in memory function (see Bremner et al., Chapter 12, in this volume). Anxiolysis may reduce or prevent the development of dissociative states, facilitating reflective reevaluation of information related to the trauma.

Once hyperarousal is controlled, a second challenge faced by clinicians is to reduce amnesia for traumatic events. Almost every psychotherapeutic strategy for treating acute psychological trauma has as a goal the integration of the traumatic experience within the conscious life of patients (Freud and Breuer 1892/1953; Krystal 1988). This task is difficult if patients are amnestic for the trauma. Several guided recollection strategies have been employed to facilitate patients' access to traumatic memories, including relaxation training, free association, dream interpretation, hypnosis, and narcosynthesis (Bartemeier et al. 1946; Grinker and Spiegel 1943; Keane et al. 1989; Krystal 1988). Each of these processes takes advantage of an altered state of consciousness, associated with increased suggestibility, in which there is a reduction in functions usually associated with the frontal cortex, such as reflection, self-monitoring, and editing of thought (Stuss 1992).

A potential risk associated with conducting guided recollection while the patient is in a compromised state is that ideas introduced by the clinician may be more readily incorporated into the memo-

ries of the patient. For example, under hypnosis or during cannabis intoxication, a subject may not be able to monitor accurately the source or validity of recalled memories (Laurence and Perry 1983; Pfefferbaum et al. 1977). Concerns about "false memories" are particularly relevant to narcosynthesis or other techniques in which the therapist recreates the roles of people within the patient's traumatic memory in order to facilitate memory retrieval (Grinker and Spiegel 1943, 1945). Furthermore, the use of pharmacological agents, such as Amytal, in narcosynthesis may produce amnesia for remembered information (Ghoneim et al. 1984). Because a patient may not fully recall information produced during narcosynthesis at later times (Grinker 1944), narcosynthesis may be best viewed as an information-gathering procedure.

Once an individual has access to memories of the trauma, what can the patient and clinician do with them to reduce the incidence of intrusive memories or flashbacks? Most patients are tormented by the intrusion of traumatic memories, and for these individuals, merely reviewing them an additional time is not necessarily therapeutic. Freud and Breuer (1892/1953) initially suggested two strategies for reducing dissociative or conversion symptoms associated with hysteria: abreaction and the formation of new associations to the traumatic memories. By abreaction, Freud and Breuer meant the discharge, during therapy, of stored feelings that could not be adequately expressed at the time of the trauma. This hydraulic view of emotions largely has been abandoned (Krystal 1978). Alternatively, modern cognitive, behavioral, and insight-oriented therapies focus on altering cognitive, affective, and identity-related associations to the trauma (Foa et al. 1989; Keane et al. 1989; Krystal 1988). Psychotherapy may help to reduce the intrusiveness and distress related to traumatic memories by altering associations to the traumatic events, essentially changing the meaning of the trauma to the individual.

Managing the recollection of traumatic memories, dissociative states, and intense affects is a tremendous challenge to the clinician treating PTSD patients. Guided reexperiencing of the trauma could evoke dissociative states that interfere with associative learning and with generalizing therapeutic gains beyond the clini-

cal setting. Intense emotions evoked during such recollections could reinforce the association between traumatic memories and intolerable intense emotions, sensitizing patients to reminders, promoting a sense of helplessness or other negative appraisals of the trauma, and making patients more reluctant or unable to review traumatic material in subsequent therapy sessions (Pitman et al. 1991). Furthermore, by stimulating intense emotional responses and negative associations in some individuals, flooding may exacerbate depression or provoke impulsive behavior, including substance abuse (Pitman et al. 1991). These potential problems help to explain the need for extensive relaxation training prior to the initiation of guided reexposure therapies such as flooding (Keane et al. 1989). This step is probably a useful adjunct to all psychotherapies for PTSD patients (Hickling et al. 1986). Furthermore, one must carefully consider the level of arousal associated with guided recollection of traumatic memories and the patient's capacity to process the information. When in the course of a therapy session a patient provides clinical data consistent with the induction of dissociative states, further efforts to encourage him or her to process traumatic material seem unlikely to be fruitful.

The concern that interference with higher cognitive functions limits the clinical utility of altered states of consciousness applies equally to proposed pharmacological adjuvants to psychotherapy, such as the serotonergic hallucinogens (compare Freedman 1968) and NMDA antagonists (compare Krystal et al. 1994b). Particularly in patients with chronic PTSD who have been in treatment for many years, there seems to be little benefit in guiding them to reexperience the trauma at the expense of repeated dissociative episodes. Carefully conducted flooding therapy, preceded by relaxation training, may reduce intrusive symptoms of PTSD but has no beneficial impact on numbing or avoidance (Keane et al. 1989). Keane et al. (1989) highlight significant psychological and social deficits that impair treatment response in patients with chronic PTSD. Thus, treatments aimed at reevaluating traumatic memories may have an important but focused role in their therapy. In addition, research is needed to characterize optimal strategies for integrating pharmacotherapy approaches

with these cognitive and behavioral psychotherapies.

If, analogous to relaxation training, pharmacological strategies were developed that preserved cognitive functions despite strong affects and traumatic memories, the formation of new associations to traumatic memories might proceed more effectively and rapidly. Benzodiazepines, reportedly useful in treating some PTSD symptoms in patients with dissociative disorders (Loewenstein et al. 1988), might help by reducing affective distress, although their amnestic properties might be counterproductive at high doses. Alternatively, one could evaluate pharmacological approaches to enhancing cognitive processing. Drugs that facilitate NMDA receptor function via enhancement of the glycine site, such as cycloserine or milacemide (Saletu et al. 1986; B. L. Schwartz et al. 1991), should be evaluated for antidissociative and other cognitive enhancing properties in PTSD patients.

Antidepressants are the best studied pharmacotherapy for PTSD, and research suggests that they provide a moderate degree of relief from flashbacks and intrusive memories. Case reports suggest that tricyclic antidepressants may reduce flashbacks, night terrors, and distress related to intrusive memories of the trauma (Burnstein 1983; Marshall 1975). Similar findings have been reported in open-label trials of monoamine oxidase inhibitors (Hogben and Cornfield 1981; Lerer et al. 1987) and serotonin reuptake blockers (Davidson et al. 1991; McDougle et al. 1991; Nagy et al. 1993). Placebo-controlled trials of tricyclic antidepressants and monoamine oxidase inhibitors have supported the findings from the open-label trials, although variability between studies and small effect sizes have limited the optimism regarding the efficacy of these agents (Davidson et al. 1990; Kosten et al. 1991; Lerer et al. 1987; Reist et al. 1989). The few studies that reported reexperiencing symptoms individually indicated that antidepressants were most effective in reducing the intrusion of traumatic memories and nightmares and less effective in reducing dissociative phenomena such as flashbacks and amnesia (Lerer et al. 1987; Nagy et al. 1993). Case reports also support the use of serotonin reuptake blockers for other dissociative disorders (Fichtner et al. 1992; Hollander et al. 1990), although fluoxetine has been reported to exac-

erbate dissociative symptoms in some patients (Black and Wojcieszek 1991). The disparity between dissociative and other intrusive symptoms may indicate that antidepressants reduce flashbacks as a secondary consequence of the other effects of these drugs. One mechanism possibly related to the efficacy of these agents is their capacity to prevent or reduce the consequences of noradrenergic hyperreactivity in PTSD patients (Krystal et al. 1989). This hypothesis is consistent with the capacity of fluoxetine treatment to block yohimbine-induced panic attacks in patients with panic disorder (Goddard et al. 1993). The limited efficacy of agents based on monoaminergic transmission suggests that a new direction is need in the development of pharmacotherapies for dissociative disorders. This new direction may be based in the pharmacology of excitatory amino acid neurotransmission implicated in the genesis of dissociative states.

Carbamazepine also has shown utility in reducing hyperarousal, sleep disturbance, and flashbacks in some PTSD patients (Lipper et al. 1986). Despite limited investigation, carbamazepine has received particular attention because of its capacity to suppress a form of neural sensitization, kindling, that may provide a cellular model for the sensitization to repeated stressors (Post and Weiss 1989). Further studies with anticonvulsant agents appear to be warranted.

Cognitive-enhancing pharmacotherapies, such as arginine vasopressin, have been suggested as treatments for memory deficits associated with PTSD (Pitman 1989). Cognitive-enhancing pharmacotherapeutic strategies might be beneficial in reducing encoding deficits associated with short-term memory impairment in PTSD patients. Drugs that might be evaluated for this purpose include ones that facilitate glutamate and acetylcholine function, such as the glycine partial agonist, cycloserine (Jones et al. 1991), and the cholinesterase inhibitor, tacrine (K. L. Davis et al. 1992). Vasopressin has been used to facilitate memory retrieval in patients with PTSD (Pitman et al. 1993), based on preclinical studies suggesting that vasopressin may enhance memory consolidation and retrieval in animals. However, the preclinical foundation of the vasopressin studies has been questioned because subsequent

studies have suggested that the promnestic effects of exogenous administration of this hormone are attributable to its enhancement of arousal (Dawson et al. 1992).

Cognitive-enhancing agents do not appear to be the appropriate pharmacotherapeutic approach for reducing amnesia for the trauma. Posttraumatic amnesia appears to arise from the suppression of retrieval rather than from an ongoing memory encoding deficit. There is no evidence to suggest that tacrine or cycloserine reduces the integrity of memory repression. Agents that do appear to facilitate the recollection of traumatic memories, such as lactate, yohimbine, vasopressin, and m-CPP, reduce posttraumatic amnesia via facilitating state-dependent retrieval. However, the sedative-hypnotic agents are the most commonly employed agents for this purpose, combined with some form of guided recollection, such as the Amytal interview.

Conclusion

Dissociative states have received relatively little attention from neurobiologists. However, the initial pharmacological challenge studies suggest that many neurotransmitter systems play important modulatory roles in the pathological development of dissociative states, as in PTSD. Glutamate systems are critically involved in the cortical and limbic circuitry of sensory processing, attention regulation, and strategic memory retrieval. Recent studies, employing ketamine, suggest that deficits in NMDA receptor function may produce dissociation-like states in healthy individuals. Further characterization of the neurobiology of these functions may facilitate the development of antidissociative pharmacotherapies.

References

Aggleton JP, Mishkin M: Projection of the amygdala to the thalamus in the cynomologous monkey. J Comp Neurol 222:56–68, 1984

Aggleton JP, Desimone R, Mishkin M: The origin, course and termination of the hippocampothalamic projections in the macaque. J Comp Neurol 243:409–421, 1986

Ahern GL, Herring AM, Tackenberg J, et al: The association of multiple personality and temporolimbic epilepsy: intracarotid amobarbital test observations. Arch Neurol 50:1020–1025, 1993

Amaral DG, Cowan WM: Subcortical afferents to the hippocampal formation in the monkey. J Comp Neurology 189:573–591, 1980

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised. Washington, DC, American Psychiatric Association, 1987

Baddeley AD: Working Memory. New York, Oxford University, 1986

Baddeley AD, Wilson B: Frontal amnesia and the dysexecutive syndrome. Brain Cogn 7:212–230, 1988

Baldwin M: Electrical stimulation of the mesial temporal region, in Electrical Studies on the Unanesthetized Brain. Edited by Ramey ER, O'Doherty DS. New York, Hoeber, 1960, pp 159–176

Bartemeier LH, Kubie LS, Menninger KA, et al: Combat exhaustion. J Nerv Ment Dis 104:489–525, 1946

Bench CJ, Frith CD, Grasby PM, et al: Investigations of the functional anatomy of attention using the Stroop test. Neuropsychologia 31:907–922, 1993

Bexton WH, Heron W, Scott TH: Effects of decreased variation in the sensory environment. Canadian Journal of Psychology 8:70–76, 1954

Black DW, Wojcieszek J: Depersonalization syndrome induced by fluoxetine. Psychosomatics 32:468–469, 1991

Bremner JD, Southwick S, Brett E, et al: Dissociation and posttraumatic stress disorder in Vietnam combat veterans. Am J Psychiatry 149: 328–332, 1992

Bremner JD, Steinberg M, Southwick SM, et al: Use of the Structured Clinical Interview for DSM-IV Dissociative Disorders for systematic assessment of dissociative symptoms in posttraumatic stress disorder. Am J Psychiatry 150:1011–1014, 1993

Bremner JD, Krystal JH, Southwick SM, et al: Noradrenergic mechanisms in stress and anxiety, I: preclinic studies. Synapse 23:28–38, 1996a

Bremner JD, Krystal JH, Southwick SM, et al: Noradrenergic mechanisms in stress and anxiety, I: clinical studies. Synapse 23:39–51, 1996b

Bremner JD, Mazure CM, Putnam FW, et al: Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). Journal of Traumatic Stress, in press

Bromberg W: Marihuana: a psychiatric study. JAMA 113:4–12, 1939

Burnstein AT: Treatment of flashbacks by imipramine. Am J Psychiatry 140:509–512, 1983

Buzsáki G, Kennedy B, Solt VB, et al: Noradrenergic control of thalamic oscillation: the role of α_2 receptors. Eur J Neurosci 3:222–229, 1990

Cappon D, Banks R: Studies in perceptual distortion. AMA Archives of Neurology and Psychiatry 10:99–104, 1960

Cappon D, Banks R: Orientational perception: a review and preliminary study of distortion in orientational perception. Arch Gen Psychiatry 5:380–392, 1961

Carlson EB, Putnam FW: Integrating research on dissociation and hypnotizability: are there two pathways to hypnotizability? Dissociation 2:32–38, 1989

Carlsson M, Carlsson A: Schizophrenia: a subcortical neurotransmitter imbalance syndrome? Schizophr Bull 16:425–432, 1990

Charney DS, Heninger GR, Breier A: Noradrenergic function in panic anxiety: effects of yohimbine in healthy subjects and patients with agoraphobia and panic disorder. Arch Gen Psychiatry 41:751–763, 1984

Charney DS, Woods SW, Goodman WK, et al: Serotonin function in anxiety, II: effects of the serotonin agonist m-CPP in panic disorder patients and healthy subjects. Psychopharmacology 92:14–24, 1987

Charney DS, Deutch AY, Krystal JH, et al: Psychobiologic mechanisms of posttraumatic stress disorder. Arch Gen Psychiatry 50:294–305, 1993

Christianson SÅ: Emotional stress and eyewitness testimony: a critical review. Psychol Bull 112:284–309, 1992

Christianson SÅ, Loftus EF: Remembering emotional events: the fate of detailed information. Cognition and Emotion 5: 81–108, 1991

Clugnet MC, LeDoux J: Synaptic plasticity in fear conditioning circuits: induction of LTP in the lateral nucleus of the amygdala by stimulation of medial geniculate body. J Neurosci 10:2818–2824, 1990

Cohen BD, Luby ED, Rosenbaum G, et al: Combined sernyl and sensory deprivation. Compr Psychiatry 1:345–348, 1960

Collins GGS, Anson J: Effects of barbiturates on responses evoked by excitatory amino acids in slices of rat olfactory cortex. Neuropharmacology 26:161–171, 1987

Corssen G, Domino EF: Dissociative anesthesia: further pharmacologic studies and first clinical experience with phencyclidine derivative CI-581. Anesth Analg 45:29–40, 1966

Costa E, Guidotti A: Neuropeptides as cotransmitters: modulatory effects at GABAergic synapses, in Psychopharmacology: The Third Generation of Progress. Edited by Meltzer HY. New York, Raven, 1987, pp 425–435

Davidson JRT, Kudler HS, Smith RD, et al: Treatment of post-traumatic stress disorder with amitriptyline and placebo. Arch Gen Psychiatry 47:259–266, 1990

Davidson JRT, Roth S, Newman E: Fluoxetine in post-traumatic stress disorder. J Trauma Stress 4:419–423, 1991

Dawson GR, Heyes CM, Iverson SD: Pharmacological mechanisms and animal models of cognition. Behavioral Pharmacology 3:285–297, 1992

Davis KL, Thal LJ, Gamzu ER, et al: A double-blind, placebo-controlled multicenter study of tacrine for Alzheimer's disease. N Engl J Med 327:1253–1259, 1992

Davis M: The role of the amygdala in fear-potentiated startle: implications for animal models of anxiety. Trends Pharmacol Sci 13:35–41, 1992

Dingledine R, Hynes MA, King GL: Involvement of *N*-methyl-D-aspartate receptors in epileptiform bursting in the rat hippocampal slice. J Physiol (Lond) 380:175–189, 1986

Dittrich A, Bättig K, von Zeppelin I: Effects of (-)Δ^9-transtetrahydrocannabinol (Δ^9-THC) on memory, attention and subjective state: a double blind study. Psychopharmacologia (Berl) 33:369–376, 1973

Domino EF, Chodoff P, Corssen G: Pharmacologic effects of CI-581, a new dissociative anesthetic, in man. Clin Pharmacol Ther 6:279–291, 1965

Dorow R, Horowski R, Paschelke G, et al: Severe anxiety induced by FG7142, a β-carboline ligand for the benzodiazepine receptor. Lancet 2:98–99, 1983

Eldridge JC, Landfield PW: Cannabinoid interactions with glucocorticoid receptors in rat hippocampus. Brain Res 534:135–141, 1990

Erickson MH: Hypnotic treatment techniques for the therapy of acute psychiatric disturbances in war. Am J Psychiatry 101:668–672, 1945

Feigenbaum JJ, Bergmann F, Richmond SA, et al: Nonpsychotropic cannabinoid acts as a functional *N*-methyl-D-aspartate receptor blocker. Proc Natl Acad Sci U S A 86:9584–9587, 1989

Felder CC, Briley EM, Axelrod J, et al: Anandamide, an endogenous cannabimimetic eicosanoid, binds to the cloned human cannabinoid receptor and stimulates receptor-mediated signal transduction. Proc Natl Acad Sci USA 90:7656–7660, 1993

Ferrer-Allado T, Brechner VL, Dymond A, et al: Ketamine-induced electroconvulsive phenomena in the human limbic and thalamic regions. Anesthesiology 38:333–344, 1973

Fichtner CG, Horevitz RP, Braun BG: Fluoxetine in depersonalization disorder. Am J Psychiatry 149:1750–1751, 1992

Fisher C, Byrne J, Edwards A, et al: A psychophysiological study of nightmares. J Am Psychoanal Assoc 18:747–782, 1970

Fisher C, Kahn E, Edwards A, et al: A psychophysiological study of nightmares and night-terrors, I: physiological aspects of the stage 4 night terror. J Nerv Ment Dis 157:75–98, 1973

Fitzgerald SG, Gonzalez E: Dissociative states induced by relaxation training in a PTSD combat veteran: failure to identify trigger mechanisms. J Trauma Stress 7:111–116, 1994

Foa EB, Steketee G, Olasov Rothbaum B: Behavioral/cognitive conceptualizations of post-traumatic stress disorder. Behavior Therapy 20:155–176, 1989

Freedman DX: On the use and abuse of LSD. Arch Gen Psychiatry 18: 330-347, 1968

Freedman DX: LSD: the bridge from human to animal, in Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives. Edited by Jacobs BL. New York, Raven, 1984, pp 203–226

Freud S, Breuer J: On the psychical mechanism of hysterical phenomena (1892), in Sigmund Freud, M.D., LL.D.: Collected Papers, Vol 1. Edited by Jones E. London, Hogarth Press, 1953, pp 24–41

Gabriel M, Sparenborg S: Posterior cingulate cortical lesions eliminate learning-related unit activity in the anterior cingulate cortex. Brain Res 409:151–157, 1987

Gabriel M, Sparenborg SP, Stolar N: Hippocampal control of cingulate cortical and anterior thalamic information processing during learning in rabbits. Exp Brain Res 67:131–152, 1987

Gabriel M, Vogt BA, Kubota Y, et al: Training-stage related neuronal plasticity in limbic thalamus and cingulate cortex during learning: a possible key to mnemonic retrieval. Behav Brain Res 46:175–185, 1991

Gaffan D, Murray EA: Amygdalar interaction with the mediodorsal nucleus of the thalamus and the ventromedial prefrontal cortex in stimulus-reward associative learning in the monkey. J Neurosci 10:3479–3493, 1990

Gaffan D, Murray EA, Fabre-Thorpe M: Interaction of the amygdala with the frontal lobe in reward memory. Eur J Neurosci 5:968–975, 1993

Geiselman RE, Bjork RA, Fishman DL: Disrupted retrieval in directed forgetting: a link with posthypnotic amnesia. J Exp Psychol Gen 112: 58–72, 1983

Geschwind N: The organization of language and the brain. Science 170: 940–944, 1970

Geschwind N: Neurological knowledge and complex behaviors. Cognitive Sciences 4:185–193, 1980

Ghoneim MM, Mewaldt SP: Benzodiazepines and human memory: a review. Anesthesiology 72:926–938, 1990

Ghoneim MM, Hinrichs JV, Mewaldt SP: Dose-response analysis of the behavioral effects of diazepam, I: learning and memory. Psychopharmacology 82:291–295, 1984

Giguere M, Goldman-Rakic PS: Mediodorsal nucleus: areal, laminar, and tangential distribution of afferents and efferents in the frontal lobe of rhesus monkeys. J Comp Neurol 277:195–213, 1988

Gloor P, Olivier A, Quesney LF, et al: The role of the limbic system in experiential phenomena of temporal lobe epilepsy. Ann Neurol 12: 129–144, 1982

Goddard A, Woods SW, Sholomskas DE, et al: Effects of the serotonin reuptake inhibitor fluvoxamine on yohimbine-induced anxiety in panic disorder. Psychiatry Res 48:119–133, 1993

Goldman-Rakic PS: Circuitry of primate prefrontal cortex and regulation of behavior by representational memory, in Handbook of Physiology, Section I: Higher Functions of the Brain. Edited by Plum F. New York, Oxford University Press, 1987, pp 373–417

Goldman-Rakic PS, Porrino LJ: The primate mediodorsal (MD) nucleus and its projections to the frontal lobe. J Comp Neurol 242:535–560, 1985

Greenberg R, Pearlman CA, Bampel D: War neuroses and the adaptive function of REM sleep. Br J Med Psychol 45:27–33, 1972

Grinker RR: Treatment of war neuroses. JAMA 126:142–145, 1944

Grinker RR, Spiegel JP: War Neuroses in North Africa. New York, Josiah Macy Jr Foundation, 1943

Grinker RR, Spiegel JP: War Neuroses. Philadelphia, Blakiston, 1945

Gruzelier J, Warren K: Neuropsychological evidence of reductions on left frontal tests with hypnosis. Psychol Med 23:93–101, 1993

Guilleminault C, Quera-Salva M-A, Goldberg MP: Pseudo-hypersomnia and pre-sleep behavior with bilateral paramedian thalamic lesions. Brain 116:1549–1563, 1993

Hafez A, Metz L, Lavie P: Long-term effects of extreme situational stress on sleep and dreaming. Am J Psychiatry 144:344–347, 1987

Halgren E, Walter RD, Cherlow DG, et al: Mental phenomena evoked by electrical stimulation of the human hippocampal formation and amygdala. Brain 101:83–117, 1978

Heaton RK: Subject expectancy and environmental factors as determinants of psychedelic flashback experiences. J Nerv Ment Dis 161:157–165, 1975

Heaton RK: Wisconsin Card Sorting Test. Odessa, TX, Psychological Assessment Resources, 1985

Herkenham M, Lynn AB, Little MD, et al: Cannabinoid receptor localization in brain. Proc Natl Acad Sci U S A 87:1932–1936, 1990

Hickling EJ, Sison GFP Jr, Vanderploeg RD: Treatment of posttraumatic stress disorder with relaxation and biofeedback training. Biofeedback Self Regul 11:125–134, 1986

Hogben GL, Cornfield RB: Treatment of war neurosis with phenelzine. Arch Gen Psychiatry 38:440–445, 1981

Hollander E, Liebowitz MR, Decaria C, et al: Treatment of depersonalization with serotonin uptake blockers. J Clin Psychopharmacol 10: 200–203, 1990

Hollister LE: Health aspects of cannabis. Pharmacol Rev 38:2–20, 1986

Horowitz MJ: Flashbacks: recurrent intrusive images after the use of LSD. Am J Psychiatry 126:565–569, 1969

Horowitz MJ, Adams JE, Rutkin BB: Visual imagery on brain stimulation. Arch Gen Psychiatry 19:469–486, 1968

Javitt DC, Zukin SR: Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 148:1301–1308, 1991

Jones RW, Wesnes KA, Kirby J: Effects of NMDA modulation in scopolamine dementia. Ann N Y Acad Sci 640:241–244, 1991

Kales JD, Kales A, Soldatos CR, et al: Night terrors: clinical characteristics and personality patterns. Arch Gen Psychiatry 37:1413–1417, 1980

Kardiner A: Psychosomatic Monographs II-III: The Traumatic Neuroses of War. Washington, DC, National Research Council, 1941

Kardiner A, Spiegel H: War Stress and Neurotic Illness. New York, Hoeber, 1947

Keane TM, Fairbank JA, Caddell JM, et al: Implosive (flooding) therapy reduces symptoms of PTSD in Vietnam combat veterans. Behavior Therapy 20:245–260, 1989

Kirk T, Roache JD, Griffiths RR: Dose-response evaluation of the amnestic effects of triazolam and pentobarbital in normal subjects. J Clin Psychopharmacol 10:160–167, 1990

Klee GD: Lysergic acid diethylamide (LSD-25) and ego functions. Arch Gen Psychiatry 8:57–70, 1963

Kluft RF: An update on multiple personality disorder. Hospital and Community Psychiatry 38:363–373, 1987

Kopelman MD, Christensen H, Puffett A, et al: The great escape: a neuropsychological study of psychogenic amnesia. Neuropsychologia 32: 675–691, 1994

Kosten TR, Krystal JH: Biological mechanisms in post traumatic stress disorder: relevance for substance abuse. Recent Dev Alcohol 6: 49–68, 1988

Kosten TR, Frank JB, Dan E, et al: Pharmacotherapy for posttraumatic stress disorder using phenelzine or imipramine. J Nerv Ment Dis 179:366–370, 1991

Kramer TH, Buckhout R, Eugenio P: Weapon focus, arousal, and eyewitness memory: attention must be paid. Law and Human Behavior 14:167–184, 1990

Krupitsky EM: Ketamine psychedelic therapy (KPT) of alcoholism and neuroses. Multidisciplinary Association for Psychedelic Studies Newsletter 3:24–28, 1972

Krystal H: Massive Psychic Trauma. New York, International Universities Press, 1968

Krystal H: Trauma and affects. Psychoanal Stud Child 33:81–116, 1978

Krystal H: Integration and Self-Healing: Affect, Trauma, Alexithymia. Hillsdale, NJ, Analytic Press, 1988

Krystal JH, Woods SW, Hill CL, et al: Characteristics of self-defined panic attacks, in 1988 New Research Programs and Abstracts (NR 263). Washington, DC, American Psychiatric Association, 1988

Krystal JH, Kosten TR, Perry BD, et al: Neurobiological aspects of PTSD: review of clinical and preclinical studies. Behavior Therapy 20:177–198, 1989

Krystal JH, Woods SW, Hill CL, et al: Characteristics of panic attack subtypes: assessment of spontaneous panic, situational panic, sleep panic, and limited symptom attacks. Compr Psychiatry 32:474–478, 1991

Krystal JH, Karper LP, Bennett A, et al: Modulation of frontal cortical function by glutamate and dopamine antagonists in healthy subjects and schizophrenic patients: a neuropsychological perspective. Neuropsychopharmacology 10 (suppl 3):230S, 1994a

Krystal JH, Karper LP, Seibyl JP, et al: Subanesthetic effects of the NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine effects. Arch Gen Psychiatry 51:199–214, 1994b

Krystal JH, Bennett A, Bremner JD, et al: Toward a cognitive neuroscience of dissociation and altered memory functions in post-traumatic stress disorder, in Neurobiological Consequences of Stress from Adaptation to Post-Traumatic Stress Disorder. Edited by Friedman M, Charney DS, Deutch AY. New York, Raven, 1995, pp 239–270

Laplane D, Degos JD, Baulac M, et al: Bilateral infarction of the anterior cingulate gyri and the fornices: report of a case. J Neurol Sci 51: 289–300, 1981

Laurence J-R, Perry C: Hypnotically created memory among highly hypnotizable subjects. Science 222:423–524, 1983

Lavie P, Hertz G: Increased sleep motility and respiration rates in combat neurotic patients. Biol Psychiatry 14:983–987, 1979

LeDoux JE: Emotion, in Handbook of Physiology: The Nervous System. Edited by Plum VF. Washington, DC, American Physiological Society, 1987, pp 419–459

LeDoux JE, Farb CR: Neurons of the acoustic thalamus that project to the amygdala contain glutamate. Neurosci Lett 134:145–149, 1991

Lerer B, Bleich A, Kotler M, et al: Post-traumatic stress disorder in Israeli combat veterans: effect of phenelzine treatment. Arch Gen Psychiatry 44:976–981, 1987

Lewis DA, Hayes TL, Lund JS, et al: Dopamine and the neural circuitry of primate prefrontal cortex: implications for schizophrenia research. Neuropsychopharmacology 6:127–134, 1992

Liebert RS, Werner H, Wapner S: Studies on the effects of lysergic acid diethylamide (LSD-25). AMA Archives of Neurology and Psychiatry 79:580–584, 1958

Lilly JC: Mental effects of reduction of ordinary levels of physical stimuli on intact healthy persons. Psychiatry Res 5:1–9, 1956

Lipper S, Davidson JRT, Grady TA, et al: Preliminary study of carbamazepine in post-traumatic stress disorder. Psychosomatics 27: 849–854, 1986

Llinás RR, Paré D: Of dreaming and wakefulness. Neuroscience 44: 521–535, 1991

Loewenstein RJ, Hornstein N, Farber B: Open trial of clonazepam in the treatment of post-traumatic stress symptoms in multiple personality disorder. Dissociation 1:3–12, 1988

Luby ED, Cohen BD, Rosenbaum G, et al: Study of a new schizophrenomimetic drug—sernyl. AMA Archives of Neurology and Psychiatry 81:363–369, 1959

Ludwig AM: "Psychedelic" effects produced by sensory overload. Am J Psychiatry 128:1294–1297, 1972

Mahowald MW, Schenck CH: Status dissociatus: a perspective on states of being. Sleep 14:69–79, 1991

Marshall JR: The treatment of night terrors associated with the posttraumatic syndrome. Am J Psychiatry 132:293–295, 1975

Mathew RJ, Wilson WH, Humphreys D, et al: Depersonalization after marijuana smoking. Biol Psychiatry 33:431–441, 1993

McCormick DA: Neurotransmitter actions in the thalamus and cerebral cortex and their role in the neuromodulation of thalamocortical activity. Prog Neurobiol 39:337–388, 1992

McCormick DA, Wang Z: Serotonin and noradrenaline excite GABAergic neurons of the guinea pig and cat nucleus reticularis thalami. J Physiol (Lond) 442:235–255, 1991

McDougle CJ, Southwick SM, Charney DS, et al: An open trial of fluoxetine in the treatment of posttraumatic stress disorder. J Clin Psychopharmacol 11:325–327, 1991

McGee R: Flashbacks and memory phenomena: a comment on "flashback phenomena-clinical and diagnostic dilemmas." J Nerv Ment Dis 172:273–278, 1984

Melges FT, Tinklenberg JR, Hollister LE, et al: Temporal disintegration and depersonalization during marihuana intoxication. Arch Gen Psychiatry 23:204–210, 1970

Mesulam MM: Dissociative states with abnormal temporal lobe EEG: multiple personality and the illusion of possession. Arch Neurol 38: 176–181, 1981b

Moghaddam B, Bolinao ML: Stimulatory effects of sub-anesthetic doses of ketamine, a psychotogenic NMDA receptor antagonist, on the outflow of dopamine and glutamate in the prefrontal cortex. Society for Neuroscience Abstracts 20:(#524.12), 1994

Morgan WW, Bermudez J, Chang X: The relative potency of pentobarbital in suppressing the kainic acid or the *N*-methyl-D-aspartic acid-induced enhancement of cGMP in cerebellar cells. Eur J Pharmacol 204:335–338, 1991

Moscovitch M: Confabulation and the frontal systems: strategic versus associative retrieval in neuropsychological theories of memory, in Varieties of Memory and Consciousness: Essays in Honour of Endel Tulving. Edited by Roediger HL III, Craik FIM. Hillsdale, NJ, Lawrence Erlbaum, 1989, pp 133–160

Moscovitch M: Memory and working-with-memory: a component process model based on modules and central system. Journal of Cognitive Neurosciences 4:257–267, 1992

Nagy LM, Morgan CA III, Southwick SM, et al: Open prospective trial of fluoxetine for posttraumatic stress disorder. J Clin Psychopharmacol 13:107–113, 1993

Nicholls DG: The glutamatergic nerve terminal. Eur J Biochem 212:613–631, 1993

Olsen RW: GABA-benzodiazepine-barbiturate receptor interactions. J Neurochem 37:1–13, 1981

Orona E, Gabriel M: Multiple-unit activity of the prefrontal cortex and mediodorsal thalamic nucleus during acquisition of discriminative avoidance behavior in rabbits. Brain Res 263:295–312, 1983

Oswald I, Evans J: On serious violence during sleep-walking. Br J Psychiatry 147:688–691, 1985

Paller KA: Recall and stem-completion priming have different electrophysiological correlates and are modified differentially by directed forgetting. J Exp Psychol Learn Mem Cogn 16:1021–1032, 1990

Pardo JV, Pardo PJ, Janer KW, et al: The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. Proc Natl Acad Sci U S A 87:256–259, 1990

Penfield W, Perot P: The brain's record of auditory and visual experience: a final summary and discussion. Brain 86:595–696, 1963

Pfefferbaum A, Darley CF, Tinklenberg JR, et al: Marijuana and memory intrusions. J Nerv Ment Dis 165:381–386, 1977

Pitman RK: Posttraumatic stress disorder, conditioning and network theory. Psychiatric Annals 18:182–189, 1988

Pitman RK, Altman B, Greenwald E, et al: Psychiatric complications during flooding therapy for posttraumatic stress disorder. J Clin Psychiatry 52:17–20, 1991

Pitman RK, Orr SP, Lasko NB: Effects of intranasal vasopressin and oxytocin on physiologic responding during personal combat imagery in Vietnam veterans with posttraumatic stress disorder. Psychiatry Res 48:107–117, 1993

Pitts FN, McClure JN: Lactate metabolism in anxiety neurosis. N Engl J Med 277:1329–1336, 1967

Post RM, Weiss SRB: Sensitization, kindling, and anticonvulsants in mania. J Clin Psychiatry 59 (suppl):23–30, 1989

Prevett MC, Duncan JS, Jones T, et al: Demonstration of thalamic activation during typical absence seizures using $H_2{}^{15}O$ and PET. Neurology 45:1396–1402, 1995

Rainey JM Jr, Aleem A, Ortiz A, et al: A laboratory procedure for the induction of flashbacks. Am J Psychiatry 144:1317–1319, 1987

Randall PK, Bremner JD, Krystal JH, et al: Effects of the benzodiazepine antagonist, flumazenil, in PTSD. Biol Psychiatry 38:319–324, 1995

Rasmussen K, Glennon RA, Aghajanian GK: Phenethylamine hallucinogens in the locus coeruleus: potency of action correlates with rank order of 5-HT_2 binding affinity. Eur J Pharmacol 32:79–82, 1986

Reist C, Kauffmann CD, Haier RJ, et al: A controlled trial of desipramine in 18 men with posttraumatic stress disorder. Am J Psychiatry 146: 513–516, 1989

Rodin E, Luby E: Effects of LSD-25 on the EEG and photic evoked responses. Arch Gen Psychiatry 14:435–441, 1966

Rosen H., Meyers HJ: Abreaction in the military setting. AMA Archives of Neurology and Psychiatry 57:161–172, 1947

Sacks O: The Man Who Mistook His Wife for a Hat. New York, Summitt Books, 1985

Saletu B, Grünberger J, Linzmayer L: Acute and subacute CNS effects of milacemide in elderly people: double-blind placebo-controlled quantitative EEG and psychometric investigations. Archives of Gerontology and Geriatrics 5:165–181, 1986

Salloway S, Southwick S, Sadowsky M: Opiate withdrawal presenting as posttraumatic stress disorder: a case of malingering following the L'Ambiance Plaza Building disaster. Hospital and Community Psychiatry 41:666–667, 1990

Sargent W, Slater E: Acute war neuroses. Lancet 2:1–2, 1940

Savage C: Variations in ego feeling induced by D-lysergic acid diethylamide (LSD-25). Psychoanal Rev 42:1–16, 1955

Schwartz BL, Hashtroudi S, Herting RL, et al: Glycine prodrug facilitates memory retrieval in humans. Neurology 41:1341–1343, 1991

Schwartz ML, Dekker JJ, Goldman-Rakic PS: Dual mode of corticothalamic synaptic termination in the mediodorsal nucleus of the rhesus monkey. J Comp Neurol 309:289–304, 1991

Sheldon PW, Aghajanian GK: Excitatory responses to serotonin (5-HT) in neurons of the rat piriform cortex: evidence for mediation by 5-HT_{1C} receptors in pyramidal cells and 5-HT_2 receptors in interneurons. Synapse 9:208–218, 1991

Southwick SM, Krystal JH, Morgan A, et al: Yohimbine and m-chlorophenylpiperazine in PTSD, in 1991 New Research Programs and Abstracts (NR 348). Washington, DC, American Psychiatric Association, 1991

Southwick SM, Krystal JH, Morgan CA, et al: Abnormal noradrenergic function in post-traumatic stress disorder. Arch Gen Psychiatry 50: 266–274, 1993

Spiegel D: Neurophysiological correlates of hypnosis and dissociation. J Neuropsychiatry Clin Neurosci 3:440–445, 1991

Stanton MD, Mintz J, Franklin RM: Drug flashbacks, II: some additional findings. International Journal of Addictions 11:53–69, 1976

Starke K, Borowski E, Endo T: Preferential blockade of presynaptic α-adrenoceptors by yohimbine. Eur J Pharmacol 34:385–388, 1975

Steriade M, Deschenes M: The thalamus as a neuronal oscillator. Brain Res Brain Res Rev 8:1–63, 1984

Steriade M, Llinás RR: The functional states of the thalamus and the associated neuronal interplay. Physiol Rev 68:649–741, 1988

Steriade M, McCarley RW: Brainstem Control of Wakefulness and Sleep. New York, Plenum, 1990

Steriade M, Datta S, Paré D, et al: Neuronal activities in brain-stem cholinergic nuclei related to tonic activation in thalamocortical systems. J Neurosci 19:2541–2559, 1990

Strassman RJ, Qualls CR, Uhlenhuth EH, et al: Dose-response study of *N,N*-dimethyltryptamine in humans, II: subjective effects and preliminary results of a new rating scale. Arch Gen Psychiatry 51:98–108, 1994

Stuss DT: Biological and psychological development of executive function. Brain Cogn 20:8–23, 1992

Swanson LW: A direct projection from Ammon's horn to prefrontal cortex in the rat. Brain Res 217:150–154, 1981

Taylor J (ed): Selected Writings of John Hughlings Jackson on Epilepsy and Epileptiform Convulsions. London, Hodder and Stroughton, 1931

Titeler M, Lyon RA, Glennon RA: Radioligand binding evidence implicates the brain 5-HT_2 receptor as a site of action for LSD and phenylisopropylamine hallucinogens. Psychopharmacology 94:213–216, 1988

Turner BH, Herkenham M: Thalamoamygdaloid projections in the rat: a test of the amygdala's role in sensory processing. J Comp Neurol 313:295–325, 1991

van der Kolk B, Blitz R, Burr W, et al: Nightmares and trauma: a comparison of nightmares after combat with lifelong nightmares in veterans. Am J Psychiatry 141:187–190, 1984

Vogt BA, Rosene DL, Pandya DN: Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey. Science 204:205–207, 1979

Whitty CWM, Lewin W: Vivid day-dreaming: an unusual form of confusion following anterior cingulectomy. Brain 80:72–76, 1957

Wilson FAW, Scalaidhe SPO, Goldman-Rakic PS: Dissociation of object and spatial processing domains in primate prefrontal cortex. Science 260:1955–1958, 1993

Woods SW, Charney DS, Silver JM, et al: Benzodiazepine receptor responsivity in panic disorder, II: behavioral, biochemical, and cardiovascular responses to the benzodiazepine receptor antagonist flumazenil. Psychiatry Res 36:115–127, 1991

Yamakura T, Mori H, Masaki H, et al: Different sensitivities of NMDA receptor channel subtypes to non-competitive antagonists. Neuroreport 4:687–690, 1993